Effects of the Benzodiazepine Antagonist Flumazenil in PTSD

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Objective: *Evidence from preclinical and clinical studies suggests a role for alterations in the benzodiazepine/$GABA_A$ receptor complex in stress and anxiety. Flumazenil is a relatively pure benzodiazepine/$GABA_A$ antagonist with limited intrinsic activity. In panic disorder patients, but not healthy controls, flumazenil has been demonstrated to provoke panic attacks.* Method: *Vietnam combat veterans with PTSD (n = 14) received 90-second intravenous infusions of flumazenil 2 mg or placebo in a double-blind, crossover study design. PTSD symptomology was assessed using the PTSD Symptom Scale, and anxiety symptoms were measured with visual analogue rating scales.* Results: *There was no significant difference in PTSD and anxiety symptoms between administration of flumazenil and placebo.* Conclusion: *Flumazenil administration does not produce an increase in anxiety and PTSD symptoms in patients with PTSD. This suggests that PTSD and panic disorder are dissimilar in terms of benzodiazepine/$GABA_A$ system function.*

Key Words: PTSD, flumazenil, GABA, benzodiazepine antagonist, stress, anxiety

Introduction

The discovery of specific binding sites for benzodiazepines in rat and human brain was an important development for the study of anxiety disorders (Squires and Braestrup 1977). Since then, the clinical potencies of benzodiazepines have been demonstrated to correlate with their affinities for the receptor. For instance, alprazolam possesses higher affinity for the receptor than diazepam, resulting in greater clinical potency (Lippa et al 1978; Braestrup et al 1983; Nutt and Lister 1988). A new class of compounds, the inverse agonists, was discovered to bind to the benzodiazepine receptor and produce anxiogenic and proconvulsant effects (Braestrup and Nielsen 1981; Braestrup et al 1982; Petersen and Jensen 1984; Barbaccia et al 1986; Hantraye et al 1987; Dorow et al 1983). In addition, Hunkeler et al (1981) described a third class of compounds, the benzodiazepine antagonists, which block the effects of both agonists and inverse agonists but have few intrinsic effects when administered alone (e.g., flumazenil) (Nutt et al 1982; Nutt and Costello 1988; Haefely et al 1992).

The inescapable stress paradigm has been proposed as an animal model of posttraumatic stress disorder (PTSD) (Krystal et al 1989; Charney et al 1993). Evidence from preclinical studies suggests that alterations in the benzodiazepine/$GABA_A$ receptor complex can occur in response to stress and anxiety (Robertson et al 1978; Insel et al 1984; Ninan et al 1982; Biggio et al 1984; Havoundjian et al 1986). Acute stress in the form of foot shock and swim stress

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(Weizman et al 1989, 1990; Medina 1983a, 1983b, Drugan et al 1986) but not defeat stress (Miller et al 1987) has been associated with a decrease in benzodiazepine binding (B_{max}) in the cerebral cortex, frontal cortex, hippocampus, and hypothalamus but not in the cerebellum, midbrain, pons, striatum, and thalamus. Chronic stress in the form of foot shock (Braestrup et al 1981) and swim stress (Weizman et al 1989, 1990) but not immobilization stress (Braestrup et al 1981) has also been associated with a decrease in benzodiazepine binding in the cerebral cortex, frontal cortex, hippocampus, and hypothalamus, but not the pons, with conflicting results in cerebellum, midbrain, and striatum. In addition, alterations in memory manifested by deficits in maze escape behaviors have been reported in rodents following exposure to inescapable stress and are prevented by pretreatment with benzodiazepines (Drugan et al 1984). These findings support the hypothesis that stress may produce abnormalities of benzodiazepine receptor function (Tallman et al 1980; Charney et al 1993).

Clinical evidence also supports a relationship between alterations in benzodiazepine receptor function and anxiety. Studies have shown the efficacy of benzodiazepines in the treatment of a variety of anxiety disorders, particularly generalized anxiety disorder, panic disorder (Roy-Byrne and Lydiard RB 1989), and symptoms of hyperarousal in PTSD (Braun et al 1990). One study (Roy-Byrne et al 1990) found reduced sensitivity to benzodiazepine effects on saccades in panic disorder, suggesting reduced sensitivity to agonists in this group.

The pharmacological challenge paradigm has been utilized in the study of benzodiazepine receptor function in anxiety. The benzodiazepine antagonist flumazenil has been reported to be panicogenic in patients with panic disorder but not in healthy controls (Nutt et al 1990a; Woods et al 1991). Since flumazenil is relatively devoid of intrinsic activity, its capacity to stimulate anxiety in panic patients raised the possibility that it blocked the actions of endogenous benzodiazepine agonist (DeBlas 1988) or that it acted more as an inverse agonist. Findings in panic disorder may be relevant to PTSD, because panic disorder is often comorbid with PTSD (Sierles et al 1983), and because of the possibility of common elements in the pathophysiology of PTSD and panic disorder (Charney et al 1984, 1987, 1993; Bremner et al 1992; Southwick et al 1993).

The purpose of this study was to compare the effects of flumazenil to placebo in PTSD patients. We hypothesized that administration of flumazenil to PTSD patients would be associated with an increase in anxiety and symptoms of PTSD compared to placebo.

Methods and Materials

Subjects

Fifteen male Vietnam combat veterans with PTSD who were inpatients at the Clinical Neuroscience Division of the National Center for PTSD, located in the Department of Veteran Affairs Medical Center at West Haven, Connecticut, gave voluntary written informed consent for participation in the study. One subject who did not complete the study had an anxiety reaction after the flumazenil infusion. All subjects were Vietnam combat veterans who met DSM-III-R criteria for chronic PTSD (APA 1987) on the basis of a structured clinical interview, either the Structured Clinical Interview for DSM-III-R (SCID; (Spitzer et al 1989) or the Modified Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L; (Endicott and Spitzer 1978). For two patients who did not complete a diagnostic interview, their diagnoses were based on consensual agreement between the investigator (PKR) and the patients' clinician. To support the validity of clinical diagnosis, all subjects had a Mississippi Scale for Combat-Related PTSD (Keane et al 1988) score greater than 107 (mean 14.1 ± 16.1 SD). The criteria for inclusion in the study were: male sex, ability to give informed consent, and absence of major medical illness, including having a history of epilepsy. The patients ranged in age from 42–51 years old. Patients with schizophrenia, schizoaffective disorder, and organic mental disorder were excluded. All subjects were free from benzodiazepines for at least 3 months by patient's report and as confirmed by clinical records and the treating physician.

Additionally, all subjects were free of other psychotropic medication for at least 7 days prior to the study and reported that they abstained from alcohol and illicit drugs for at least 1 month prior to the study. Absence of substance abuse was supported by random urine toxicology screens and breathalizer examinations conducted by the inpatient treatment program.

Patients who had a structured diagnostic interview (12/14) were included in comorbidity analyses. Nine out of 12 patients (75%) met criteria for lifetime history of panic disorder, with or without agoraphobia, and 8/12 patients (67%) for current panic disorder; 10/12 patients (83%) met criteria for lifetime history of major depression, and 9/12 patients (75%) for current major depression. Current dependence was defined as meeting dependence criteria during the 6 months prior to entry into the study. Twelve out of 12 patients (100%) met criteria for lifetime history of alcohol dependence, and 8/12 patients (67%) for current alcohol dependence; 3/12 patients (25%) met criteria for lifetime history of sedative dependence and 0/12 (0%) for current sedative dependence; 4/12 patients (33%) met criteria for lifetime history of cocaine dependence and 0/12 (0%) for current cocaine dependence.

Flumazenil Test Procedures

The methodology of the flumazenil challenge paradigm is similar to that described in a previous published report (Nutt

et al 1990a). Since flumazenil has been reported to have few intrinsic effects when administered alone to healthy subjects (Nutt et al 1982), we compared effects of flumazenil versus placebo within PTSD without utilization of a control group. On the test day, an intravenous cannula was inserted in an antecubital vein. Patients remained in a semisupine position throughout the testing, except to use the bathroom. Each patient received two infusions, flumazenil 2 mg IV and an equal volume of saline (0.9% USP NaCl) placebo in a double-blind, within-subject design with the order of administration randomized. The active medication was administered to 10 patients during the first session and five patients during the second session. Both infusions were administered over 90 seconds. The first infusion was administered 45 minutes after insertion of the cannula. The second infusion, either saline or flumazenil, was given 100 minutes after the first. The half-life of flumazenil is approximately 50 minutes. A previous report demonstrated that a 60-minute period between challenges was sufficient to limit carryover effects (Nutt et al 1990a).

Physiological and Biochemical Methods

An automated sphygmomanometer (Dinemap) was used to record blood pressure and heart rate measurements. The blood pressure and the heart rate were recorded 5 minutes prior to the infusion and at the following time points: 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, and 90 minutes after the infusion. Plasma cortisol levels were measured by radioimmunoassay kits (Incstar Cooperation; Stillwater, MN); intra- and interassay CVs were 3% and 5%, respectively. Specimens were assayed in duplicate to reduce variance in method. Individual values reported are means from these specimens.

Behavioral Ratings

Behavioral measures included the Visual Analogue Scales (VASs), the Panic Attack Symptom Scale (PASS), and the PTSD Symptom Scale (Southwick et al 1993). the VASs are used to rate anxiety, fear, and nervousness. Scores could range from 0 mm (not at all) to 100 mm (most ever). The Panic Attack Symptom Scale is a 27-item inventory for DSM-III-R (APA 1987) symptoms associated with panic that rates severity of symptoms on a scale from 0 (not at all) to 4 (severe). Scores on the PASS range from a minimum of 27 to the maximum of 108. The following criteria were used to determine whether a patient had a panic attack during the test: 1) an increase of 25% or greater from baseline on the VAS for anxiety; 2) increase in severity of 4 or more DSM-III-R panic attack symptoms from baseline, as measured on the PASS; and 3) for patients with a history of panic attacks, the induced panic attack must be qualitatively similar to the patient, as the naturally occurring anxiety states.

The PTSD symptom scale rates PTSD symptom severity on a five-point scale. Scores can range from a minimum of 14 to a maximum of 70 on this scale. The following 14 symptoms comprise the scale: intrusive traumatic thoughts, flashback, startle, hypervigilant, distant from people, out of body, emotionally numb, difficulty concentrating, guilt, grief, helpless, sad, hopeless, and anger. We have previously shown an increase in PTSD symptoms and anxiety utilizing these instruments, the PTSD Symptom Scale and the PASS, in psychopharmacological studies (Southwick et al 1993).

Data Analysis

The data were analyzed using the Statistical Analysis System (SAS Institute 1982). The effects of flumazenil on cardiovascular measures, behavioral ratings, and plasma cortisol levels were initially analyzed using an analysis of variance (ANOVA) with repeated measures using two within-subject factors, drug (placebo vs. flumazenil) and time of the measurement. Order effects were entered as a factor in the repeated measures ANOVAs.

Results

Behavioral Effects

Flumazenil failed to produce anxiogenic effects in the PTSD patients. There was no difference in anxiety, fear, or nervousness as measured by the Visual Analogue Scales between administration of flumazenil and placebo and no significant increase from baseline following administration of flumazenil (Table 1). Panic attacks occurred at equal frequency after administration of flumazenil and placebo (1/14; 7%).

There was no difference in panic attack symptoms as measured by the Panic Attack Symptom Scale following administration of flumazenil in comparison to placebo and no significant increase from baseline with flumazenil. Similarly, there was no difference in PTSD symptoms as measured by the PTSD Symptom Scale between administration of flumazenil and placebo and no significant increase from baseline following administration of flumazenil (Figure 1). Flashbacks occurred after flumazenil in 1/14 (7%) patients and after placebo in none of the patients. In addition, when the subject that finished only the active infusion was included in an analysis of the active drug group alone, there was not a significant increase from baseline in either anxiety, as measured by the Panic Attack Symptom Scale, or PTSD symptoms, as measured by the total score on the PTSD Symptom Scale. Order effects were entered as a factor in the repeated measures ANOVAs and not found to be significant.

Physiological Effects

Flumazenil did not affect diastolic blood pressure (DBP) or heart rate (HR) relative to placebo. When the effects of

Table 1. The Effects of Intravenous Flumazenil and Placebo on Visual Analogue Scale scores in Posttraumatic Stress Disorder Patients ($n = 14$)[a]

	Placebo			Flumazenil		
	Baseline	10 min	30 min	Baseline	10 min	30 min
Fear	8.00 ± 4.00	11.00 ± 5.00	3.00 ± 1.00	8.00 ± 5.00	8.00 ± 3.00	5.00 ± 2.00
Nervousness	22.00 ± 6.00	18.00 ± 4.00	10.00 ± 4.00	20.00 ± 7.00	23.00 ± 5.00	13.00 ± 4.00
Anxiety	23.00 ± 6.00	26.00 ± 5.00	11.00 ± 3.00	20.00 ± 6.00	31.00 ± 8.00	16.00 ± 6.00

Values are expressed as mean ± standard error (SE).
[a]Scores for fear, nervousness, and anxiety were not significantly different following flumazenil administration relative to placebo.

flumazenil and placebo on systolic blood pressure (SBP) were examined, there was a main effect for time ($F = 2.17$; $df = 12, 156$; $p = .01$) with a trend for a drug by time interaction ($F = 1.61$; $df = 12, 156$; $p = .09$).

Effects on Cortisol

Flumazenil had no effect on cortisol levels.

Discussion

The benzodiazepine antagonist flumazenil does not have anxiogenic effects in patients with PTSD. Symptoms of PTSD, panic attack severity, anxiety, fear, nervousness, serum cortisol levels, and physiological responses were not found to be increased after administration of flumazenil relative to placebo.

A previous study utilizing the same dose and route of administration of flumazenil in panic disorder reported flumazenil to be panicogenic in patients with panic disorder compared to controls. In this report, panic disorder was a current comorbid diagnosis in 67% (8/12), and patients who also met criteria for panic disorder did not have a panicogenic effect from flumazenil. Unlike findings for noradrenergic systems where PTSD and panic disorder patients both have panic attacks following yohimbine (Southwick et al 1993), the current data suggest that panic disorder in the presence of PTSD may be dissimilar to primary panic disorder in terms of regulation of benzodiazepine/$GABA_A$ function.

There are several competing hypotheses for alterations in benzodiazepine receptor function in anxiety. Patients with anxiety disorders may have an altered "set-point" of the benzodiazepine receptor, causing antagonists that have little intrinsic effect in healthy controls to be shifted toward the inverse agonist direction (Nutt et al 1990b). Flumazenil-induced panic attacks could also reflect an endogenous benzodiazepine agonist withdrawal state. Flumazenil precipitates withdrawal symptoms in animals chronically treated with benzodiazepine agonists (Lukas and Griffiths 1982). Flumazenil could stimulate this "withdrawal-like" syn-

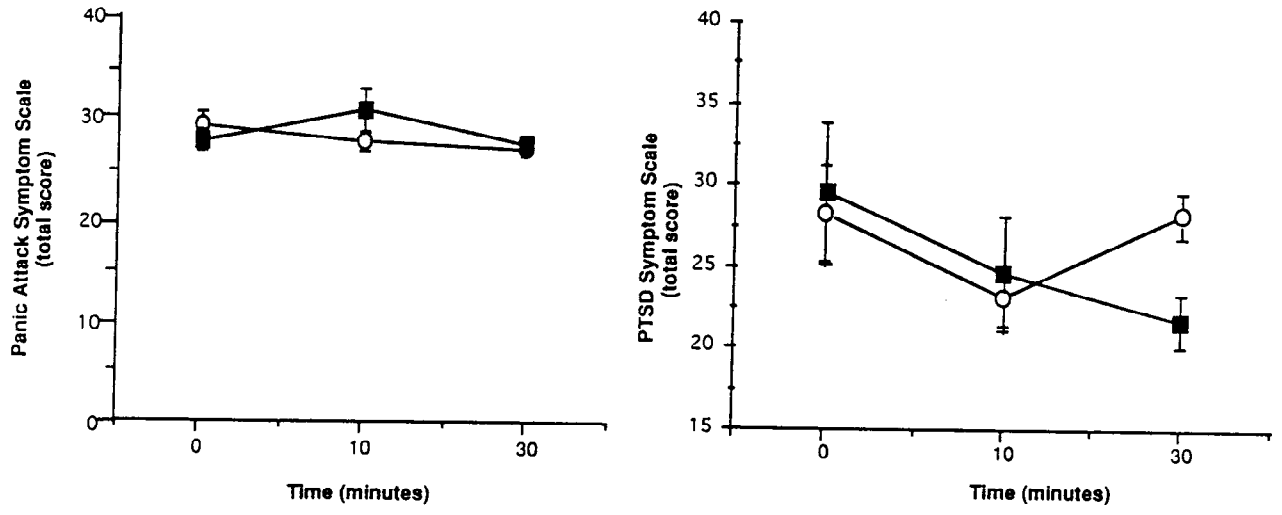

Figure 1. The effects of intravenous administration of flumazenil *(closed squares)* and placebo *(open circles)* ± SE on total scores of the Panic Attack Symptom Scale (PASS) and the Posttraumatic Stress Disorder Symptom Scale in 14 patients with posttraumatic stress disorder (PTSD). There was no difference in scores on the PASS or the PTSD Symptom Scale following administration of flumazenil in comparison to placebo.

drome in panic patients through: 1) overproduction of an endogenous benzodiazepine agonist, and/or 2) altered benzodiazepine receptor gene structure or regulation of benzodiazepine gene expression. The overlap between flumazenil-induced anxiety and panic disorder is supported by well-documented similarities between benzodiazepine withdrawal and panic attacks in panic disorder patients (Tyrer et al 1983). It is unlikely that flumazenil-induced panic would arise from overproduction of an inverse agonist, since flumazenil would be predicted to block inverse agonist-induced anxiety. It is also unlikely that underproduction of agonists or inverse agonists would increase flumazenil sensitivity, since both conditions would be predicted to produce compensatory increases in agonists (or inverse agonist) sensitivity and to reduce antagonist effects.

Our results should be interpreted with caution due to several possible limitations. Flumazenil and placebo infusions were both administered on the same day; however, we found no evidence for carryover effects. The patients who participated in the study were treatment-seeking combat veterans with PTSD, and the results from this study may not be applicable to acute PTSD or to non-treatment seeking populations. In addition, we compared the effects of flumazenil versus placebo within PTSD without utilization of a control group. Previous studies report the lack of intrinsic activity of flumazenil in healthy subjects (Nutt et al 1982; Nutt et al 1990b); therefore, we did not use a control group.

Since flumazenil failed to produce an increase in anxiety or exacerbation of PTSD symptoms, this study did not provide evidence that PTSD is associated with overproduction of an endogenous agonist; however, alternative hypotheses could not be ruled out by this study: 1) PTSD is associated with an overproduction of inverse agonist compounds, or 2) PTSD is associated with underproduction of endogenous agonist compounds. Further investigation of these hypotheses is indicated. Flumazenil was used as a probe of the benzodiazepine/$GABA_A$ receptor complex; however, this compound has been reported to have few intrinsic effects in healthy controls. Agents with more provocative actions on benzodiazepine neuronal activity may be more revealing. For example, the effects of partial inverse agonists such as iomazenil on PTSD symptoms should be explored (Schubinger et al 1991; Johnson et al 1990). In addition, brain imaging methods are now available to measure the density of the benzodiazepine receptors (Innis et al 1991).

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